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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,107	01/03/2006	Hiroyuki Kanoh	Q92075	1089

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EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,107	KANOH ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 17, 18, and 21-24 are pending in this application.

2. Cancellation of claims 1-16, 19, and 20 is acknowledged.

3. Claims 17, 18, and 21-24 are examined.

Priority

4. Applicant's submission of a certified English translation of Japanese application No. JP 2003-189837, filed in Japan on July 1, 2003 and to which Applicants claim priority under 35 U.S.C. 119, is duly noted.

Information Disclosure Statement

5. Foreign patent documents JP 2001-163862, JP 2001-507338, JP 2002-541095, JP 2004-2318, and JP 2004-504351, previously not considered, have now been considered only to the extent that they are cited on the search report of the corresponding International application of the instant application, and/or to the extent that they have an English abstract or English counterpart. A signed IDS indicating said consideration is filed herewith.

Claim Rejections - 35 USC § 112

6. The rejection of claim 23 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's amendment to claim 23.

7. The rejection of claims 17 and 18 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's amendments to claims 17 and 18.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **Claims 17, 18, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of bone mass and bone strength, does not reasonably provide enablement for preventing a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of bone mass and bone strength.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir.1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors have been considered and are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to preventing or treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength, or both of bone mass and bone strength. The relative skill of those in the art is high, that of an MD or PHD. That

factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites a UW Medicine website (http://www.orthop.washginton.edu/uw/tabID_3426/Default.aspx), which generally teaches that metabolic bone diseases are caused by problems with mineral metabolism, nutrition, and genetic diseases. It is noted that genetic diseases cannot be prevented.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prevention" as "to keep from happening or existing", i.e., to completely eradicate. The claims are thus very broad insofar as they recite the "preventing" of a metabolic bone disease, i.e., the complete eradication of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the prevention of a metabolic bone disease. No reasonably specific guidance is provided concerning useful therapeutic protocols for preventing or treating a metabolic bone disease, other than a general teaching of "prevent effect" (for example, page 51), which does not enable one skilled in the art to make or use the invention . The latter is corroborated by the working examples.

4. The quantity of experimentation necessary

Because of the known unpredictability in the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for preventing a metabolic bone disease as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

5. Suggested alternative language

Since the term “treating” is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies (active), the examiner recommends deleting the term “preventing” and simply reciting “treating” instead.

Response to Arguments

10. Applicant's arguments filed 9/16/08 have been fully considered but they are not persuasive.

Applicants argue that it is understood that an agent which can treat the cause of osteoporosis is useful in both of treatment and prevention of the disease, and those of ordinary skill in the art understand that the agent can be used for both purposes. Applicants cite four references and several patents in support of said position.

This argument is not persuasive because the instant application does not provide a nexus between treating and preventing a metabolic bone disease, for reasons stated above, and the references cited by Applicant do not provide support that the agents of the instant application are enabled for preventing a metabolic bone disease. Additionally, the prosecution history of any application is decided on a case-by-case basis, and the patents cited by Applicants do not provide support that the agent of the instant application are enabled for preventing a metabolic bone disease.

Claim Rejections - 35 USC § 103

11. The rejection of claims 17, 18, and 21-24 under 35 U.S.C. 103(a) as being unpatentable over Igarashi et al (US Patent 7,173,033) in view of Burk (US Patent 6,174,857) is withdrawn in view of Applicant's arguments that the Igarashi et al patent does not have the effective filing date of the parent International application because said international application was not published in English, and in view of Applicant's certified translation of the priority document, thus perfecting priority of the instant application.

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. **Claims 17, 18, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burk (US Patent 6,174,857)**.

The claimed invention is drawn to a method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of

bone mass and bone strength, which comprises administering to a patient an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately (see claim 17).

Burk teaches a method for treatment of osteoporosis in mammals comprising administering a pharmaceutical preparation comprising IGF-1 (abstract). The pharmaceutical preparation may contain further pharmaceutically valuable substances, especially estrogen and bisphosphonates (col. 4, lines 38-44). The term “osteoporosis” reasonably reads on “a metabolic bone disease which accompanies reduction of the bone mass, bone strength, or both of bone mass and bone strength”. Additionally, the term "estrogen" would reasonably include all forms of estrogen, including synthetic estrogen, and therefore reasonably reads on “non-living body-derived non-peptide osteoblast differentiation promoting compound”.

Burk does not specifically teach that the combination of estrogen and bisphosphonate is used in the pharmaceutical preparation.

However, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to include both estrogen and bisphosphonate in the pharmaceutical preparation; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation of success, because Burk fairly teaches and suggests that the pharmaceutical preparation may contain further pharmaceutically valuable substances (plural), and thus it would be within the purview of the skilled artisan to select the combination of estrogen and bisphosphonate by

routine experimentation, in order to optimize the efficacy of the resultant preparation for treating osteoporosis.

Regarding claim 18, Burk teaches that the treatment of osteoporosis includes Type II osteoporosis (see column 1).

Regarding claim 23, Burk et al teach that the bisphosphonate used is particularly 3-aminopropyl-1-hydroxy-1,1-bisphosphonate (col. 4, lines 42-43), which is pamidronate.

14. **Claims 17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoshino et al (US Patent 5,910,492), as evidenced by Tenenbaum (*Bone*, Vol. 13, pp. 249-255, 1992)**.

The claimed invention is drawn to a method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of bone mass and bone strength, which comprises administering to a patient an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately (see claim 17).

Hoshino et al teach osteogenic promoting pharmaceutical compositions used as a prophylactic/therapeutic agent for various bone diseases (abstract). The composition comprises non-peptide osteogenic promoting substances (col. 1, lines 59-65) such as those listed in Hoshino et al (see col. 4, lines 20-41); said list includes bisphosphonic acids (col. 4, lines 38-39). Hoshino et al further teach that the pharmaceutical

composition may contain more than one non-peptide osteogenic promoting substance (col. 4, lines 42-44).

Hoshino et al do not specifically teach the combination of a non-peptide osteogenic promoting substance and a bisphosphonate compound.

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select a non-peptide osteogenic promoting substance and a bisphosphonate compound as the substances in the pharmaceutical composition; thus arriving at the claimed invention. One skilled in the art would have been motivated to do so, with a reasonable expectation of success, because Hoshino et al fairly teach and suggest that the pharmaceutical composition may contain more than one non-peptide osteogenic promoting substance (see col. 4, lines 42-44), and thus it would be within the purview of the skilled artisan to select the combination of a non-peptide osteogenic promoting substance and a bisphosphonate compound by routine experimentation, in order to optimize the efficacy of the resultant preparation for treating various bone diseases.

Regarding claim 23, Hoshino et al teach that the bisphosphonic acid are described in Bone, vol. 13, pp. 249-255 (1992), i.e., the Tenenbaum reference (see col. 4, lines 38-39). Tenenbaum teach that bisphosphonates which promote osteogenesis include APD (see pages 249 and 254), which is pamidronate.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. **Claims 17, 18, and 21-24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 7 of U.S. Patent No. 7,173,033 in view of Burk (US Patent 6,174,859)**.

The claimed invention is drawn to a method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of bone mass and bone strength, which comprises administering to a patient an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately (see claim 17).

The '033 patent claims a method for stimulating bone formation in a mammalian animal, comprising administering an effective amount of the compound corresponding to the non-living body-derived non-peptide osteoblast differentiation promoting

compounds of the instant application (see claims 1, 5, and 7 of the '033 patent and claims 21, 22, and 24 of the instant application).

The ‘033 patent does not specifically teach the presence of a bisphosphonate compound in the composition to be administered.

Burk teaches a method for treatment of osteoporosis in mammals comprising administering a pharmaceutical preparation which includes a bisphosphonate compound (see col. 4, lines 38-44). Since osteoporosis is characterized by bone loss (see col. 1, lines 33-38), treatment of osteoporosis reasonably reads on “stimulating bone formation".

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to include a bisphosphonate compound with the compound of the ‘033 patent; thus arriving at the claimed invention. One skilled in the art would have been motivated to do so because the prior art fairly teaches and suggests that bisphosphonate compounds are known to be used in compositions administered for the treatment of osteoporosis, as taught by Burk et al. Additionally, it is prima facie obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. One would reasonably expect success from the addition of the bisphosphonate-containing composition taught by Burk et al with the compound taught by the ‘033 patent because both references are drawn to methods involving stimulation of bone formation.

Regarding claim 18, the '033 patent claims a method for stimulating bone formation, which reasonably reads on the treatment of osteoporosis, since osteoporosis is characterized by bone loss.

Regarding claim 23, Burk et al teach that the bisphosphonate used is particularly 3-aminopropyl-1-hydroxy-1,1-bisphosphonate (col. 4, lines 42-43), which is pamidronate.

Response to Arguments

17. Applicant's arguments filed 9/16/08 have been fully considered but they are not persuasive.

Applicants argue that one ordinary skill in the art would not have been motivated to modify and/or combine the references because the active agents in each reference are totally different and there is not structural similarity between these two agents. Applicants also argue that one of ordinary skill in the art would not have had a reasonable expectation of success in modifying or combining the references because the instant application is directed to a small chemical molecule osteoblast differentiating promoting compound, whereas the IGF-1 of Burk is a naturally occurring protein. This argument is not persuasive because both references are drawn to resolving the same problem of stimulating bone formation (as noted above, treatment of osteoporosis reasonably reads on stimulating bone formation, since osteoporosis is characterized by bone loss). Therefore, one skilled in the art would be motivated to combine two compositions, each of which is taught by the prior art, to be useful for the same

purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. Therefore, the combination of references renders the instant application prima facie obvious, and Applicants have not presented any evidence to the contrary.

18. Claims 17, 18, and 21-24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 7 of U.S. Patent No. 7,133,033 in view of Tenenbaum et al ("*Bone*, Vol. 13, pp. 249-255, 1992).

The claimed invention is drawn to a method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass, bone strength or both of bone mass and bone strength, which comprises administering to a patient an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately (see claim 17).

The '033 patent claims a method for stimulating bone formation in a mammalian animal, comprising administering an effective amount of the compound corresponding to the non-living body-derived non-peptide osteoblast differentiation promoting compounds of the instant application (see claims 1, 5, and 7 of the '033 patent and claims 21, 22, and 24 of the instant application).

The '033 patent does not specifically teach the presence of a bisphosphonate compound in the composition to be administered.

Tenenbaum et al teach that bisphosphonates, including APD (pamidronate), a very potent inhibitor of resorption, also has significant effects on various aspects of osteoblastic activity. At lower dosages which approximate those that might be used in vivo there appeared to be an increase in mineral accumulation relative to APD-free control, and thus APD could be used not only to promote mineralization but also to prevent resorption of newly formed bone (see pages 249 and 254).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to include a bisphosphonate in the method of the '033 patent; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because the addition of bisphosphonate results in the benefits of increased mineralization as well as prevention of resorption, as taught by Tenenbaum. One would reasonably expect success from the inclusion of bisphosphonates as taught by Tenenbaum to the method claimed by the '033 patent because both references are drawn to methods involving osteogenesis.

Regarding claim 18, the '033 patent claims a method for stimulating bone formation, which reasonably reads on the treatment of osteoporosis, since osteoporosis is characterized by bone loss.

Regarding claim 23, Tenenbaum et al teach the use of APD, which is pamidronate, for promoting osteogenesis (page 249).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611